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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/293,670	04/16/99	FISHER J	A-68104/DJB/

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EXAMINER	
WESSENDORF, T	
ART UNIT	**PAPER NUMBER**
1627	12

DATE MAILED: 07/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/293,670	Fisher et al
Examiner	**Group Art Unit**
T. Wessendorf	1627

☒ Responsive to communication(s) filed on *3/13/00*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-14* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

The continuing application of U.S. Application Serial No. 09/062,333, inserted at the first sentence of the specification has been corrected to the correct S. N. 09/062,330 as provided in the Oath or declaration.

Applicants' statement that formal drawings will be submitted upon the finding of allowable subject matter and the issuance of a notice of Allowance is noted. In the absence of said formal drawings, the objection to the drawings is maintained but will be held in abeyance. The letter to the Draftsman as to the proposed changes in the drawings is likewise noted. The proposed changes by correcting in red ink to indicate Figures 1A-1C have been forwarded and seen by the Draftsman and unacceptable for the same reasons provided in PTO 948.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the p21 as the bioactive agent for a particular cell population such as the tumor cells, does not reasonably provide enablement for a method using a library of bioactive agents or nucleic acid that encodes said bioactive agents and a population of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons advanced at pages 6-9 of the last Office action, 10/6/99.

Applicants admit that the claims are directed to a method of screening for a bioactive agent capable of altering a cellular phenotype. But argue that the claims do not require a library of bioactive agents for use and in the same breath admit that the claims include the use of a candidate bioactive agent, or libraries of bioactive agents that allows the identification of whether the candidate agent is a bioactive agent. Applicants' arguments appear contradictory. As a skilled in the art knows, screening for a compound (a bioactive agent in the instant case), could only occur when a multitude (i.e., a library) of compounds is present. (Cf. with the claims in the prior art e.g., Kamb).

It is argued that the specification provides extensive description of many compounds encompassed by the phrase candidate bioactive agent(e.g., page 16, line 8). The only description provided in the specification is an incomplete list of the compounds encompassed by the claims such as protein, small organic molecules, etc. and a generalized statement for said library of candidate bioactive agents or compounds. The list provides for a candidate agents with unrelated or a widely varied compound structures from a single organic molecule such as purines, pyrimidine to a molecule as complex as the biomolecules like proteins, polynucleotides, polysaccharides (in natural or synthetic form) or to the modified forms of said biomolecules and/or combinations of these different compounds. Not only do the compounds in the library vary in structures but also in their molecular size, concentration or amount and/or library size, etc.

It is argued that the specification makes clear that the candidate bioactive agent is not a limiting factor for the present methods because capability of the bioactive agent to alter a cellular phenotype need not be known prior to the use of the agent in the present method. While this might be so, however, the claims appear not to correspond with what is being described in the specification. There is no correspondence between the

embodiments described in the specification of a method to identify cells that have undergo alterations in cellular phenotype as determined using FACS machine and that of the claims to screen for bioactive agents that will have an affect on the cellular phenotype by altering said cellular phenotype. See e.g., page 8, lines 10-19 of the instant specification which states the "...detection of alterations in cellular phenotypes..." Therefore, the specification appears to disclose screening of cells, not bioactive compounds or agents, for cells that have undergone cellular phenotype alteration. Also, note applicants' statement(page 7, second full paragraph) in the instant REMARKS which states that "... the specification repeatedly teaches that using multiple cellular parameters to assay for alterations in cellular phenotype ....." [It is suggested that applicants make the claims commensurate with the description in the specification of detecting alterations in cellular phenotypes i.e., provide a nexus between the claims and specification. Also, to claim a method to the use of library of p21 and its mutants as the bioactive agents in tumor cell populations].

Claims 1-3 and 5-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting

as being unpatentable over claims 1-6, 12-33 and 35 of copending Application No. 09/062,330('330)for reasons of record.

Applicants' statement to hold this rejection in abeyance is noted. However, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of copending Application No.09/157,748 ('748) for reasons of record.

Applicants' statement to hold this rejection in abeyance is noted. However, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 1-7 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 09/157,748 which has a common inventor with the instant application for reasons advanced in the last Office action, pages 13-14.

Applicants argue that the copending application has only a single inventor who is also an inventor on the present application therefore, the invention disclosed in the '748 application could not have been invented by one not named as an inventor in the present application.

Applicants' argument is nothing more than a mere statement as there is no showing under 37 CFR 1.132 that the invention in the copending application was derived from the inventor of this application and is thus not the invention "by another". Thus, based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future patenting of the conflicting application.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-4, 7-10 and 13-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Nolan (WO 97/27212).

Applicants admit that Nolan teaches the separation of cells based on a single reporter gene. Nevertheless, argue that Nolan does not teach sorting cells in a FACS machine by separating

cells on the basis of at least five or at least three cellular parameters. Contrary to applicants' arguments, Nolan at e.g., page 31, line 1-5 describe a method comprising introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acid comprises a different, generally randomized nucleotide sequence, The plurality of cells is then screened for a cell exhibiting an altered phenotype. Nolan discloses that an altered phenotype is meant that the phenotype of the cell is altered in some detectable and/or measurable way that can be detected or measure by the basis of the screening methods. Such phenotypic changes include but are not limited to gross physical changes such as changes in cell morphology, cell growth , cell viability, adhesion to substrates, changes in the expression of one or more RNAs, proteins, other molecules (page 31, lines 7-26). The altered phenotype is detected in a wide variety of ways using standard cell viability assays, including both increased cell death (apoptosis) and increased cell viability (two cellular parameters) (page 31, line 28 up to page 32)standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, (third and fourth parameters) including FACS or other dye staining techniques

(fifth parameter). Furthermore at page 33, lines 19-28 Nolan describes that once a cell with an altered phenotype is detected, the cell is isolated form from the plurality which do not have altered phenotypes. This is done in any number of ways, as is known in the art, and will in some instances depend on the assy or screen. Suitable isolation techniques include FACS, expression of survival protein, (first parameter) induced expression of a cell surface protein or other molecule that can be rendered fluorescent or taggable for physical isolation; (second) death of cells (third) and isolation of DNA (fourth) or other cell viability indicator dyes, (fifth) etc. Example 1, page 51 uses FACS to analyze a fluoresceinated cell, expression of the cells, apoptosis inhibition, use of dye techniques as propidium iodide or other dyes such as ethidium bromide/acridine orange. Therefore, the broadly recited at least five cellular parameters is fully met by the specific cellular parameters as described supra.

Claims 3, 8, 10 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Kamb (5,955,275) for reasons advanced in the previous Office, paragraph bridging pages 15 and 16.

Applicants admit that Kamb teaches the use of FACS to separate cells based on the expression of a single gene.

Applicants further admit that in some instances it is expression of an inserted fluorescent gene linked to a phenotype-associated promoter, citing Example 2. Example 3 is admitted to describe the expressed cell surface gene that is detected using a fluorescently labeled antibody. But argue that Kamb does not suggest separating cells on the basis of at least 3 cellular parameters. As correctly pointed out by applicants Kamb discloses the sorting of the single expressed gene by sorting the cells based on the different cellular parameters of (1) a fluorescently labeled antibody (i.e., immunofluorescence); (2) quantifying measurement level of the expressed reporter gene (e.g., col.8, line 45 up to col. 9, line 7) and (3)the uptake of the GFP(a "vital dyes") or its emission or (4)the use of BFP. Therefore, Kamb measurement of at least three (3) specific cellular parameters by FACS machine fully meets the broadly recited (undefined) cellular parameters. Note the disclosure of Kamb of expression of reporter gene GFP as useful in monitoring living cells that act as "vital dyes" (col. 8, lines 51-63) that permits screening on a flow sorter machine such as FACS and the use of other modes of light emission, col. 7, lines 26-32. See further Kamb disclosure at e.g., col.8, lines 54-57 as to the term low sorter machine that analyzes light emission intensity from cells

or other objects and separates these cells or objects according to parameters such as light emission intensity.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5-6 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nolan or Kamb in view of Hide et al(Jrnl. of Cell Biology) for reasons advanced in the last Office action, pages 17-18.

Applicants argue that Hide does not disclose or suggest sorting cells in a FACS machine by separating cells on the basis of at least three cellular parameters and does not cure the shortcoming of Kamb or Nolan. Contrary to applicants argument Hide is combined with Kamb or Nolan for the claimed limitation of the cellular phenotype as exocytosis and measuring said cellular parameter to detect the forward and light scattering of cells to show the exocytosis effect of the cells. This attribute has been

used to classify populations of (mast) cells. Applicants cannot attack the references individually when the rejection is based on the combination of references. One having ordinary skill in the art would have been motivated to measure another cellular parameters as light scattering by FACS when the cellular phenotype is caused by exocytosis to provide a clear or discernible effect of the cell on the environment. It has been well known in the art that combinations of these different known parameters using FACS machine would lead to a clearer identification of the cellular phenotype alterations.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire

on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1627.

Certain papers related to this application may be submitted to Art Unit 1627 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 O.G. 61 (November 16, 1993) and 1157 O.G. 94 (December 28, 1993)(see 37 C.F.R. 1.6(d)). The official fax telephone numbers of the Group are (703)308-7924. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T.

Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Mon. to Fri. from 8 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat Ph.D., can be reached on (703) 308-0570.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T. Wessendorf

T. Wessendorf

Patent Examiner

Art Unit 1627

7/3/00